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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,499	02/18/2004	Michel Chateau	34076/US	6087

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EXAMINER	
SHAHNAN SHAH, KHATOL S	

ART UNIT	PAPER NUMBER
1645	

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07/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/781,499	CHATEAU ET AL.	
	Examiner	Art Unit	
	Khatol S. Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

1. The amendment filed 5/1/6/2007 has been entered into the record. Claims 1, 4, 12 and 13 have been amended.

2. Claims 1-21 are pending in this application. Claims 1-14 are under consideration. Claims 15-21 are withdrawn from further examination as being drawn to non-elected invention.

Information Disclosure Statement

3. The information disclosure statement filed 5/1/6/2007 has been considered. An initialed copy is enclosed.

Objections Withdrawn

4. Objection to the specification made in paragraph 3 of office action mailed 1/18/2007 is withdrawn in view of applicants' amendments of 5/16/2007.

Rejections Withdrawn

5. Rejection of claims 1-14 under the second paragraph of 35 U.S.C. 112, made in paragraph 10 of office action mailed 1/18/2007 is withdrawn in view of applicants' amendments of 5/16/2007.

Rejections Maintained

6. Rejection of claims 1-14 under 35 U.S.C. 101 double patenting rejection, made in paragraph 7 of office action mailed 1/18/2007 is maintained. The rejection was as stated below:

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in

scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-5 and 7-11 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1-5 and 7-11 of copending Application No. 10/546,139.

Claims 1-5 and 7-11 of this application conflict with claims 1-5 and 7-11 of Application No.10/546,139. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Applicants have requested to hold the rejection in abeyance until the first action on Application No. 10/546,139.

7. Rejection of claim 6 under non-statutory obviousness- type double patenting rejection, made in paragraph 9 of office action mailed 1/18/2007 is maintained.

The rejection was as stated below:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in

the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to

prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 6 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being Unpatentable over claims 1 and 6 of copending Application No. 10/546,139. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same method for preparation of an evolved microorganism comprising the same steps and material involved in the methods. Claim 6 of the instant application recites that modification step a) favors the reduction of NADP to NADPH. Claim 6 of the copending Application No. 10/546,139 recites the same limitation plus it recites that possibly by limiting the oxidation of NADPH to NADP. It is obvious that when reduction of reduction of NADP to NADPH occurs, oxidation of NADPH to NADP will be limited.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have requested to hold the rejection in abeyance until the first action on Application No. 10/546,139.

8. Rejection of claims 1-4 and 8-14 under 35 U.S.C. 102 (b), made in paragraph 12 of office action mailed 1/18/2007 is maintained.

The rejection was as stated below:

Claims 1-4 and 8-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamori et al. (Applied Microbial Biotechnology, vol.52, pp. 179-185, 1999).

The claims are drawn to a method for the preparation of evolved microorganisms permitting a modification of metabolic pathways, comprising the following steps: a) preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite when that microorganism is grown on a defined medium, thereby impairing the ability of that microorganism to grow; b) culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution; and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate.

Nakamori et al. teach a preparation of evolved microorganisms permitting a modification of metabolic pathways (see abstract). Nakamori et al. teach preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite (methionine) when that microorganism is grown on a defined medium, see page 180 wherein E.coli JM 109 cells in the late exponential phase in LB medium were mutagenized. Nakamori et al. produced L-methionine-analogue resistant mutants (see page 180). Nakamori et al. teach culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate, see page 180 under selection and cultivation of L-methionine-producing mutants (i.e. an evolved microorganism). Nakamori et al teach biosynthesis pathway of amino acids and methionine (see title and abstract).

Nakamori et al. also teach limitation of claims 8-14 wherein the evolved microorganism possesses at least one evolved gene coding for an evolved protein (see page 182 Introduction of the wild-type metJ gene into the L- methionine-producing strain with a mutant metJ gene and page 183 Molecular modeling of the

DNA-binding region in the mutant MetJ protein). The prior art anticipates the claimed invention.

Applicants' arguments filed5/16/2007 have been fully considered but they are not persuasive.

Applicants argue:

Nakamori reports on bacteria subjected to treatment with a mutagen, followed by selection of desired mutant bacteria using a medium containing methionine analogues. The mutations introduced into bacteria by the method of Nakamori are random rather than pathway-or gene-specific, owing to the use of mutagen, and initially generate a wide variety of mutant bacterial genotypes.

In contrast, claim 1 and dependent claims 2-4 and 8-14 of the instant application are drawn to methods for preparing an evolved microorganism, which involve a first step of producing a modified microorganism by introducing a predetermined genetic alteration, particularly a gene modification that inhibits a metabolic pathway and thereby impairs the ability of the microorganism to grow. For technical clarity, claim 1 has been currently amended to recite that the genetic modification is a "directed" genetic modification. Support for the amendment is found, for example, at page 6, paragraph 4 of the specification.

Applicant submits that Nakamori does not describe the production of modified microorganisms by directed genetic modification, i.e., introduction of predetermined genetic modifications. Accordingly, Applicant submits that Nakamori does not anticipate the currently claimed subject matter.

Further, while in Nakamori's method it is the random mutation in response to mutagen that generates a mutant having the desired phenotype and underlying genotype among a wide variety of mutants, the first step of genetic modification in the present claimed methods does not generate a microorganism having the final desired phenotype and genotype - rather, genetic modification in the present methods sets the stage for evolution to achieve a genotype (critically including an evolved gene) that exhibits the desired phenotype in a subsequent step. In particular, given the metabolic defect achieved by directed genetic modification in

the first step of the presently claimed methods, evolved microorganisms having desired metabolic properties are then selected for in a subsequent step by the application of selective pressure through the use of appropriate media. Applicant submits that Nakamori does not anticipate the instant claimed methods on this additional basis, and respectfully requests withdrawal of the rejections and allowance of the claims.

In response to applicants' arguments the office brings applicants attention to the instant specification (see page 3) following definitions:

evolved microorganism as according to the invention an '**evolved microorganism' is defined as a microorganism obtained by selection of a modified microorganism**. The evolved microorganism displays at least one difference from the modified microorganism. This difference may, for example, be the improvement of an enzymatic characteristic, or the creation of a new metabolic pathway.

According to the invention a **'metabolic pathway'** is one or more enzymatic reactions the succession of which forms a molecule (product) that is different from the starting molecule (substrate).

According to the invention a **'modification'** is a change, in **particular a deletion**, of at least one gene and/or its promoter sequence, which gene codes for an enzyme.

According to the invention a **'metabolite'** is a molecule synthesized and/or transformed by the microorganism.

Page 6 further recites "According to the invention a 'modified microorganism' is a microorganism obtained by performing controlled modifications, i.e., that are not the result of a process of evolution. Examples of such a modification are the **directed mutation or deletion of a gene, or the directed modification of a promote**r.

Therefore, according to applicants own definitions Nakamori et al. do teach a preparation of evolved microorganisms by modifying a metabolic pathways (see abstract). Nakamori et al. teach preparing a **modified microorganism by genetic modification of cells of an initial microorganism** so as to inhibit the production or consumption of a **metabolite** (methionine) when that

microorganism is grown on a defined medium, see page 180 wherein E.coli JM 109 cells in the late exponential phase in LB medium were mutagenized. Nakamori et al. produced L-methionine-analogue resistant mutants (see page 180). Therefore, Nakamura's mutation does result in a specific mutation in metabolic pathway.

9. Rejection of claims 1-7 under 35 U.S.C. 102 (b), made in paragraph 13 of office action mailed 1/18/2007 is maintained.

The rejection was as stated below:

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/177112 published 2 September 1993.

The claims are drawn to a method for the preparation of evolved microorganisms permitting a modification of metabolic pathways, comprising the following steps: a) preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite when that microorganism is grown on a defined medium, thereby impairing the ability of that microorganism to grow; b) culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution; and c) selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate.

WO 93/177112 teaches a preparation of evolved microorganisms permitting a modification of metabolic pathways i.e. biosynthesis pathway of amino acids (see abstract and amended claims). WO 93/177112 teaches preparing a modified microorganism by genetic modification of cells of an initial microorganism so as to inhibit the production or consumption of a metabolite (methionine) when that microorganism is grown on a defined medium (see claims). WO 93/177112 teaches preparing a modified microorganism by genetic modification of cells of an initial microorganism see amended claim 1. WO 93/177112 teaches culturing the modified microorganism thereby obtained on said defined medium to cause it to evolve, where the defined medium can contain a co-substrate to allow such evolution and c)

selecting a modified microorganism able to grow on said defined medium, if necessary with a co-substrate, see claims specially claim 1. WO 93/177112 teaches limitations of claims 5-7 wherein the metabolic pathway consumes NADPH (see figure 1). WO 93/177112 teaches biosynthesis pathway of amino acids, methionine (see title and abstract). The prior art anticipates the claimed invention.

Applicants' arguments filed5/16/2007 have been fully considered but they are not persuasive

Applicants argue:

WO 93/177112 describes methods for enhancing methionine production in a fermentation process by transforming a microorganism with a homoserine-activating enzyme gene and a sulfur incorporating enzyme gene. The purpose of these modifications is to improve the production ofmethionine by over-expressing genes coding for enzymes involved in the biosynthesis pathway.

WO 93/177112 does not disclose inhibiting a metabolic pathway by genetic modification to impair the ability of the microorganism to grow, thereby providing for the application of selective pressure in respect of a particular metabolic pathway on evolving, descendant microorganisms with the use of appropriate media. Quite to the contrary, WO 93/177112 teaches methods for improving a desired biosynthesis pathway in a given microorganism by making particular genetic modifications that directly effect the biosynthesis improvement.

Accordingly, Applicant submits that WO 93/177112 does not anticipate the presently claimed subject matter and respectfully requests that the rejections be withdrawn and the claims allowed.

In response to applicants' arguments the office brings applicants attention to the instant specification (see page 3) following definitions:

evolved microorganism as according to the invention an **'evolved microorganism' is defined as a microorganism obtained by selection of a modified microorganism**. The evolved microorganism displays at least one difference from the modified microorganism. This difference may, for example, be the improvement of an enzymatic characteristic, or the creation of a new metabolic

pathway.

According to the invention a **'metabolic pathway'** is one or more enzymatic reactions the succession of which forms a molecule (product) that is different from the starting molecule (substrate).

According to the invention a **'modification'** is a change, in **particular a deletion**, of at least one gene and/or its promoter sequence, which gene codes for an enzyme.

According to the invention a **'metabolite'** is a molecule synthesized and/or transformed by the microorganism.

Page 6 further recites, "According to the invention a 'modified microorganism' is a microorganism obtained by performing controlled modifications, i.e., that are not the result of a process of evolution. Examples of such a modification are the **directed mutation or deletion of a gene, or the directed modification of a promoter**.

Therefore, according to applicants own definitions WO 93/177112 teaches a preparation of evolved microorganisms permitting a **modification of metabolic pathways i.e. biosynthesis pathway of amino acids** (see abstract and amended claims). WO 93/177112 teaches preparing a **modified microorganism by genetic modification** of cells of an initial microorganism so as to inhibit the production or consumption of a **metabolite** (methionine) when that microorganism is grown on a defined medium (see claims). As to applicants arguments that WO 93/177112 only teaches enhancement not inhibition.

In response applicants' attention is drawn to the language of the WO 93/177112 abstract " and/or by modifying the methionine biosynthetic pathway" when a reduced sulfur source is used in the medium production of methionine is enhanced and when an oxidized sulfur source is used production of methionine is inhibited (see table 1, page 7).

Status of Claims

10. No claims are allowed.

Claims 1-14 stand rejected.

Claims 15-21 have withdrawn as being drawn to non-elected inventions.

Conclusion

11. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is 571-272-0863. The examiner can normally be reached on Monday-Friday 7:30 AM-5:00 PM If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew can be reached on 571-272-0787.
The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Khatol Shahnan-Shah . B.S.,
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Biotechnology Patent Examiner
Art Unit 1645
July 9, 2007

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER